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Enantioselective Alkylation of Lactams and Lactones via Lithium Enolate Formation Using a Chiral Tetradentate Lithium Amide in the Presence of Lithium Bromide

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Abstract

Enantioselective alkylation of lactams and lactones can be realized up to 98% ee by deprotonation with a chiral tetradentate lithium amide (**4b**) in the presence of lithium bromide, and subsequent alkylation with active alkylating agents in non-chelating solvents. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: Asymmetric reaction; Alkylation; Lactam; Lactone

Stereoselective carbon-carbon bond formation by alkylation of enolates provides one of the most important methodologies in organic synthesis. Although many diastereoselective alkylation reactions have been developed,[1] only limited examples of highly enantioselective reactions are known to date.[2] This is especially the case in enantioselective alkylations of amides and esters. In this paper, we report new asymmetric transformations of lactams and lactones by enantioselective alkylation of lithium enolates using a chiral tetradentate ligand in the presence of lithium bromide.

In our previous paper,[3] we reported enantioselective alkylation of a carboxylic acid using a chiral bidentate lithium amide (**3b**) as a chiral ligand. First we used **3b** in benzylation of 1-methyl-2-piperidone (**1a**)[4] (Table 1, run 1). Although the reaction proceeded moderately, no chiral induction was observed. Recently it was found that a complex composed of lithium enolate, lithium bromide, and a chiral tetradentate amine was proposed to make an effective asymmetric induction system for cyclic ketones.[2] We then tried to use a chiral tetradentate ligand in the alkylation of **1a**. Several reaction conditions were examined and the results are summarized in Table 1. When a tetradentate lithium amide (**4b**) was used instead of **3b**, the desired adduct was obtained in 24% ee (run 2). Furthermore, it was found that an addition of lithium bromide dramatically improved the enantioselectivity (run 3). These results suggest that lithium enolate, lithium bromide, and **4a** should form an appropriate chiral environment around the π face of the lithium enolate. Several solvents were examined, and 2,2,5,5-tetramethyltetrahydrofuran (TMTHF)[5] was found to give the highest enantiomeric excess (runs 3~10).[6]

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While other alkylating agents worked well under these conditions (runs 13 and 14), a slightly lower selectivity was observed in the benzylation of 1-benzyl-2-piperidone (**1b**) (run 15). A five membered ring substrate gave much lower chemical yield (run 16).

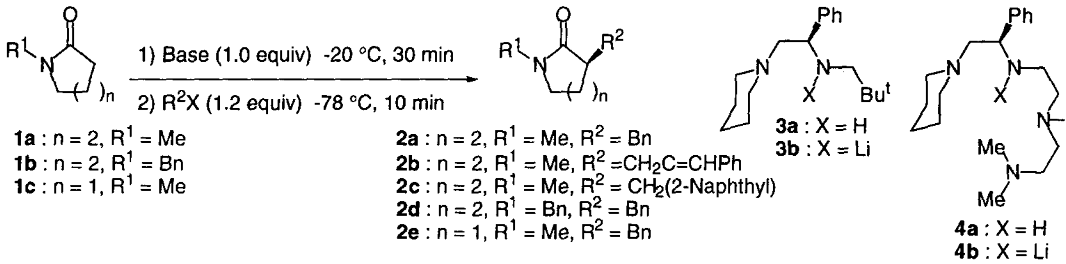


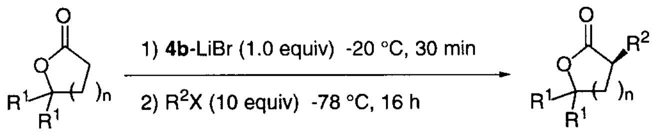
Table 1. Alkylation of Lactam Lithium Enolates

Run	Substrate	Base	Solvent	R^2X	Product[a]	Yield (%)[b]	E. e. (%)[c]
1	**1a**	**3b**	toluene	$PhCH_2Br$	**2a**	47	0
2	**1a**	**4b**	toluene	$PhCH_2Br$	*(R)*-**2a**	42	24
3	**1a**	**4b**-LiBr	toluene	$PhCH_2Br$	*(R)*-**2a**	51	94
4	**1a**	**4b**-LiBr	cumene	$PhCH_2Br$	*(R)*-**2a**	64	95
5	**1a**	**4b**-LiBr	^{t}BuOMe	$PhCH_2Br$	*(R)*-**2a**	64	93
6	**1a**	**4b**-LiBr	Et_2O	$PhCH_2Br$	*(R)*-**2a**	26	91
7	**1a**	**4b**-LiBr	THF	$PhCH_2Br$	*(R)*-**2a**	72	42
8	**1a**	**4b**-LiBr	MMTHF[d]	$PhCH_2Br$	*(R)*-**2a**	52	75
9	**1a**	**4b**-LiBr	DMTHF[e]	$PhCH_2Br$	*(R)*-**2a**	62	88
10	**1a**	**4b**-LiBr	TMTHF[f]	$PhCH_2Br$	*(R)*-**2a**	64	98
11[g]	**1a**	**4b**-LiBr	toluene	$PhCH_2Br$	*(R)*-**2a**	65	73
12[g]	**1a**	**4b**-LiBr	TMTHF[f]	$PhCH_2Br$	*(R)*-**2a**	74	89
13	**1a**	**4b**-LiBr	TMTHF[f]	$PhCH{=}CHCH_2Br$	**2b**	55	96
14	**1a**	**4b**-LiBr	TMTHF[f]	(2-Naphthyl)CH_2Br	**2c**	55	97
15[h]	**1b**	**4b**-LiBr	toluene	$PhCH_2Br$	**2d**	76	75
16	**1c**	**4b**-LiBr	toluene	$PhCH_2Br$	**2e**	7	68

[a] For the absolute configuration, see Ref 11. [b] Isolated yield. [c] Determined by HPLC analyses.
[d] 2-Methyltetrahydrofuran. [e] 2,5-Dimethyltetrahydrofuran. [f] 2,2,5,5-Tetramethyltetrahydrofuran.
[g] Alkylation time: 16h. [h] Alkylation time: 2h.

A typical experimental procedure (run 10) is as follows. Under an argon atmosphere, a solution of MeLi-LiBr in ether (1.14 *N* for MeLi and 1.25 *N* for LiBr) (0.49 mL, 0.56 mmol for MeLi and 0.61 mmol for LiBr) was added to a solution of **4a** in TMTHF (5.5 mL) at -20 °C. After 30 min, a solution of **1a** (62 mg, 0.55 mmol) in TMTHF (2 mL) was added. After stirring at -20 °C for 30 min, the mixture was cooled to -78 °C. A solution of benzyl bromide (0.08 mL, 0.67 mmol) in TMTHF (2 mL) was added, and the reaction mixture was stirred at -78 °C for 10 min. The reaction was quenched with 0.1 *N* aqueous citric acid (5 mL) and the aqueous layer was extracted with ethyl acetate (20 mL x 3). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and dried over Na_2SO_4. Evaporation of the solvents gave the crude product, which was purified by column chromatography (silica gel, hexane-acetone) to give *(R)*-**2a** (71 mg, 64% yield, 98% ee by HPLC analysis) as a colorless oil. $[\alpha]_D^{23}$ +84.7 (c 1.06, $CHCl_3$).

This approach was then applied to the alkylation of lactone enolates. The results of asymmetric alkylation of lactones using **4b** are summarized in Table 2. The lithium enolate of 5,5-dimethyl-δ-valerolactone (**5a**)[7] reacted with benzyl bromide in TMTHF to afford the alkylated adduct in 63% yield with 90% ee (run 1). The chemical yield was improved to 79%, when toluene was used as a solvent (run 2).[8] Alkylations by other active alkylating agents were then examined, and it was found that cinnamyl bromide and 2-(bromomethyl)naphthalene gave high ees, while the reaction proceeded slowly with 3-phenylpropyl iodide (runs 8~10). In benzylation of δ-valerolactone (**5b**), the reaction proceeded to give the desired product in 47% yield with 74% ee, although some side reactions occurred,[9] which were due to instability of the lithium enolate of **5b** (run 11). 4,4-Dimethyl-γ-butyrolactone (**5c**)[10] gave a lower yield (run 12), while no reaction occurred employing γ-butyrolactone (**5d**).



5a : n = 2, R^1 = Me
5b : n = 2, R^1 = H
5c : n = 1, R^1 = Me
5d : n = 1, R^1 = H

6a : n = 2, R^1 = Me, R^2 = Bn
6b : n = 2, R^1 = Me, R^2 = $CH_2CH{=}CHPh$
6c : n = 2, R^1 = Me, R^2 = CH_2(2-Naphthyl)
6d : n = 2, R^1 = Me, R^2 = $(CH_2)_3Ph$

6e : n = 2, R^1 = H, R^2 = Bn
6f : n = 1, R^1 = Me, R^2 = Bn

Table 2. Alkylation of Lactone Lithium Enolates

Run	Substrate	Solvent	R^2X	Product[a]	Yield (%)[b]	E. e. (%)[c]
1	**5a**	TMTHF	$PhCH_2Br$	(*R*)-**6a**	63	90
2	**5a**	toluene	$PhCH_2Br$	(*R*)-**6a**	79	91
3	**5a**	THF	$PhCH_2Br$	(*R*)-**6a**	91	22
4	**5a**	DME	$PhCH_2Br$	(*R*)-**6a**	86	54
5	**5a**	^tBuOMe	$PhCH_2Br$	(*R*)-**6a**	71	88
6	**5a**	Et_2O	$PhCH_2Br$	(*R*)-**6a**	74	90
7[d]	**5a**	toluene	$PhCH_2Br$	(*R*)-**6a**	74	90
8	**5a**	toluene	$PhCH{=}CHCH_2Br$	**6b**	64	85
9	**5a**	toluene	(2-Naphthyl)CH_2Br[e]	**6c**	63	90
10	**5a**	toluene	$Ph(CH_2)_3I$[f]	**6d**	14	76
11	**5b**	toluene	$PhCH_2Br$	(*R*)-**6e**	47	74
12	**5c**	toluene	$PhCH_2Br$	**6f**	28	68

[a] For the absolute configuration, see Ref. 11. [b] Isolated yield. [c] Determined by HPLC analyses. [d] Alkylation time: 1 h. [e] 1.2 equiv was used. [f] Alkylation condition: -45 °C, 5 h.

In conclusion, highly enantioselective alkylation reactions of lactam and lactone enolates using a stoichiometric amount of a chiral tetradentate ligand have been developed. Further investigations to apply this methodology to catalytic enantioselective alkylation reactions[2c] are now in progress.

References and Notes

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(5) Commercially available from Aldrich®. TMTHF can also be synthesized by refluxing a mixture of 2,5-dimethyl-2,5-hexanediol and dilute aqueous sulfuric acid.

(6) Judging from runs 3 and 11, and runs 10 and 12, prolonged reaction time caused decrease in enantioselectivity. In the case of TMTHF, less decrease was observed.

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(8) In contrast to the alkylation of **1a**, decrease in enantioselectivity was not observed under the prolonged reaction time.

(9) In THF-HMPA, high yield was realized using LDA. Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711-712.

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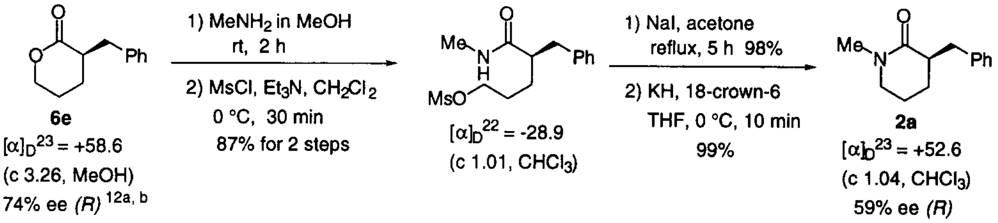
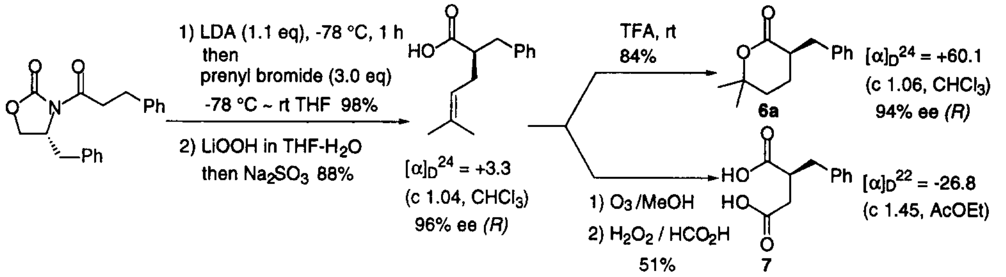
(11) The absolute configuration of **2a** was confirmed by chemical correlation from **6e**, whose absolute configuration is known.[12]



The absolute configuration of **6a** was also confirmed by chemical correlation to **7** whose absolute configuration is known.[13]



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